REMARKS

Claims 1, 2, 4-11 and 14-24 are currently pending. Claims 14-24 have been withdrawn. Claim 6 has been amended merely to overcome the Examiner's objection regarding a typographical error.

Applicants acknowledge with appreciation the Examiner's withdrawal of the previous claim rejections under 35 U.S.C. 103(a) with regard to the cited references U.S. 5,602,301 ("the '301 patent"), Robinson et al., "Implantation of Skeletal Myoblast-Derived Cells", in Cellular Cardiomyoplasty: Myocardial Repair with Cell Implantation, ed: Kao and Chiu, 1997 ("Robinson"), Murry et al., *J. Clin. Invest.* 98:2512-23 (1996) ("Murry"), Wakitani et al., *Muscle & Nerve*, 18:1417-26 (1995) ("Wakitani") and U.S. 5,736,396 ("the '396 patent").

The rejection under 35 USC 103(a) over WO 99/03973 will be discussed in detail below. Before addressing the remaining rejection specifically, applicants wish to reiterate certain background as the context for their argument in favor of the patentability of the pending claims.

It is well recognized in the art that acute myocardial injury is followed by identifiable stages of wound healing during which the cellular environment within the injured heart changes dramatically. More particularly, it is known from histological analyses that immediately after an acute myocardial injury, the myocardium becomes fragmented and necrotic. Tissue necrosis is followed by inflammation. Specifically, within about a week, most of the necrotic cardiomyocytes have disappeared and a predominantly mononuclear inflammatory infiltrate is present. By about two weeks after injury the inflammatory infiltrate disappears and the fibroblasts and collagen that comprise scar tissue become evident. At four and eight weeks after injury, the tissue is fibrotic and no longer contains cardiac muscle cells or lymphocytes. Instead, it is composed of connective tissue cells, such as fibroblasts, and non-cellular components, such as collagen and fibronectin. Cardiac scar tissue is non-contractile, and is believed to be an inert tissue having a limited blood supply.

The art cited by the Examiner does not refer to implantation of mesenchymal stem cells directly into cardiac *scar* tissue. Furthermore, given that mesenchymal stem cells are pluripotent cells which are believed to be highly sensitive to their surrounding environment, the cited art does not provide any reasonable expectation that mesenchymal stem cells could improve heart function when implanted into the inhospitable environment of cardiac scar tissue. In contrast, as will be discussed below, the cited art exemplifies administration of cells to the normal heart but does not teach or suggest that implantation of mesenchymal stem cells into cardiac *scar* tissue would result in improvement of heart function.

Regarding the rejection under 35 USC 103, applicants point out that WO 99/03973 was published on 28 January 1999. Applicants instant application was filed on July 29, 1999 but claims the benefit of two provisional applications having filing dates of April 14, 1999 and July 31, 1998. To the extent that the instant application is entitled to priority to the July 31, 1998 date, applicant contends that WO 99/03973 is not appropriately cited as art against this application. Applicant specifically points out to the Examiner, however, that WO 99/03973 has a United States counterpart which issued as U.S. Patent No. 6,387,369.

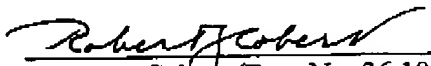
WO 99/03973 refers to mesenchymal stem cells, but does not suggest they would be capable of improving heart function after implantation into cardiac scar tissue. Specifically, WO 99/03973 (like its United States counterpart U.S. 6,387,369) refers to implantation of mesenchymal stem cells into "damaged" myocardium but never discusses the survival potential of mesenchymal stem cells implanted into *scar* tissue. Moreover, the examples are limited to implantation into normal cardiac muscle and the document as a whole teaches that "environmental signals ... act in concert with mechanical and electrical signaling *in vivo* to lead to cardiac differentiation" (see page 8, lines 28-30). Given that scar tissue would likely be devoid of mechanical or electrical signaling, applicants' discovery that mesenchymal stem cells implanted into scar tissue can actually survive and improve cardiac function would not have been expected in view of WO 99/03973.

In summary, the cited art, does not teach or suggest that implantation of mesenchymal stem cells into cardiac *scar* tissue would result in improvement of heart function. To the contrary, the teachings of the art would more readily lead to the expectation that implantation of a mesenchymal stem cell into cardiac scar tissue would not improve heart function because it would induce only the formation of additional scar tissue.

In view of the above, applicants request that the Examiner withdraw the rejections under 35 U.S.C. 103(a).

If it is believed that a discussion of these or other issues would be beneficial, the Examiner is invited to contact applicants' attorney at the number listed below.

Respectfully submitted,



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